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The Patent Office

Cardiff Road
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NP9 1RH

1. Your reference — RSJ07644GB

2. Patent application number *(The Patent Office will fill in this part)* — 0226996.7 — 19 NOV 2002

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Oxford Instruments Superconductivity Limited
Old Station Way, Eynsham
Witney, Oxford,
OX8 1TL, Great Britain

Patents ADP number *(if you know it)*

08189367001

If the applicant is a corporate body, give the country/state of its incorporation — Great Britain

4. Title of the invention — SAMPLE INSPECTION APPARATUS

5. Name of your agent *(if you have one)* — Gill Jennings & Every

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

Broadgate House
7 Eldon Street
London
EC2M 7LH

Patents ADP number *(if you know it)* — 745002

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

YES

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9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	6
Claim(s)	2
Abstract	
Drawing(s)	4 +4

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	NO

11. For the applicant
Gill Jennings & Every

I/We request the grant of a patent on the basis of this application.

Signature [signature] Date 19 November 2002

12. Name and daytime telephone number of person to contact in the United Kingdom

R.E. Skone James
020 7377 1377

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SAMPLE INSPECTION APPARATUS

The invention relates to sample inspection apparatus and in particular to nuclear magnetic resonance (NMR) inspection apparatus.

NMR has been developed over many years to enable chemical information about samples such as their structure to be obtained. This is carried out using NMR spectroscopy. The NMR process involves the generation of a high strength, uniform magnetic field within a working volume. The sample is located in the working volume and then subjected to RF irradiation causing the spins of certain nuclei to precess. On removing the RF irradiation, the spins return to their rest state and their precession frequency can be monitored thus giving an indication of structural information and the like.

In many analytical situations, other information about samples is often needed as well thus requiring additional experimental equipment to be provided. An example is Fourier Transform Ion Cyclotron Resonance Mass Spectroscopy (FTICR or FTMS). In FTICR, ions from the sample under investigation are exposed to a high strength, substantially uniform magnetic field while being rotated at high speed (experiencing cyclotron excitation) and subjected to RF irradiation.

Typically, chemical samples of very small volume are analysed, typically in the order of femtomoles.

A number of problems arise in these circumstances. Firstly, each experiment requires a high strength magnet and these are large, bulky and very expensive. In addition, problems arise when attempting to analyse the same sample in more than one way since there are risks of contamination and an inability to carry out the tests simultaneously.

In accordance with the present invention, we provide sample inspection apparatus comprising a magnet

assembly located in a cryostat and surrounding a bore at room temperature so as to define one or more working regions in the bore; a first, NMR probe which can be inserted in the bore to bring a sample into the or one of the working regions, the magnetic field in that working region having a homogeneity or profile suitable for performing a NMR experiment; and a second probe which can be inserted in the bore to bring a sample into the or another working region, the magnetic field in that working region having a homogeneity or profile suitable for performing a different experiment on the sample.

We have realised that there are significant synergies between NMR apparatus on the one hand and certain other experimental apparatus, particularly FTICR, on the other hand. Thus, both require a high strength, substantially uniform magnetic field and thus both typically need a cryostat in order to cool the windings of a magnet to low temperature to achieve superconductivity. This enables the high strength magnetic field to be generated cost effectively. Each type of apparatus uses a probe within which the sample is located in use, the probe being inserted into a room temperature bore of the cryostat.

In a first example, the magnet assembly defines two separate magnets spaced apart along the bore, each generating a uniform magnetic field within its own working region, one suitable for the NMR experiment and the other suitable for the different experiment. The advantage of this arrangement is that a single cryostat can be utilised.

In this case, the two probes can be arranged simultaneously in the bore so that both experiments can be carried out simultaneously. As will be explained in more detail below, this allows the same sample to be analysed in two different ways substantially simultaneously and avoids problems of time delay between carrying out the two experiments, contamination etc.

In more preferred arrangements, the magnet assembly comprises a single magnet and this could be wound in order to generate two separate working regions of substantially uniform magnetic field but typically will generate a single working region of substantially uniform magnetic field in the bore.

In this latter case, the probes can be inserted into the bore in turn or more preferably can be inserted from opposite ends of the bore with one probe being arranged to bring its sample into the working region followed by the other.

In a particularly preferred arrangement, the probes are constructed so that both can bring their respective samples into the same working region simultaneously. This could be achieved, for example, by making the ends of the two probes male and female so that they will interengage.

Typically, the magnet assembly will be actively shielded to reduce the fringe field strength.

Although the "different experiment" is described herein as FTICR, other experiments are also possible, namely EPR (electron paramagnetic resonance) or ESP (electron spin resonance).

Advantages of the invention include a reduced cost since only a single cryostat, and in most cases a single magnet, is required to obtain the same experimental data previously requiring two separate structures. Also the proximity or even commonality of the two working regions provides for increased sample throughput, reduced contamination, and improved confidence of data, for example when needing to process FTICR data and NMR data simultaneously particularly with respect to mass confirmation in conjunction with NMR. An example of this is the need to use NMR to obtain the 3D structure of a protein and FTICR to obtain peptide sequencing data.

Some examples of apparatus according to the present invention will now be described with reference to the accompanying drawings, in which:-

Figure 1 is a block diagram illustrating the primary components of an analytical instrument applicable to any of the examples shown in the following drawings;

Figure 2 is a longitudinal section through a first example of the sample inspection apparatus;

Figures 3A and 3B are longitudinal sections through a second example in two different conditions; and,

Figures 4A and 4B are a longitudinal section and a cross-section respectively through a third example of the apparatus.

The apparatus shown in Figure 1 comprises a conventional liquid chromatograph 1 to which a sample to be analysed is supplied. The chromatograph 1 separates out the component to be analysed which, as explained above, will be of very small volume, and this is fed to a flow splitter 2. The sample is then split with a proportion passing to NMR sample injection equipment 3 and the remaining portion to ICR mass spectrometer sample injection equipment 4. The sample from the equipment 4 is then supplied to an ICR mass spectrometer ultra high vacuum (UHV) cell 5 while the sample from the equipment 3 is passed to an NMR RF probe 6.

In operation, the cell 5 and the probe 6 will generate output signals which are captured and then processed, typically by a common microcomputer or other processor so that the results can be compared accurately and easily on the basis that the tests were carried out simultaneously on the same sample.

Figure 2 illustrates a first example of the sample inspection apparatus which can be used with the Figure 1 arrangement. The apparatus comprises a cryostat 10 of conventional form having a central liquid helium vessel 12 accessed via an access and service neck 14. This is surrounded by a gas cooled radiation shield 16 which in

turn is surrounded by a liquid nitrogen containing vessel 18. Finally, the outer wall 20 of the cryostat is separated from the liquid nitrogen vessel 18 by an evacuated chamber 22.

The cryostat surrounds a room temperature bore having a large diameter section 24 continuing into a narrower diameter section 26. An actively shielded magnet assembly 28 is located in the liquid helium vessel 12 and surrounds the bore 24,26. The magnet assembly is split into two sections, one surrounding each part of the bore 24,26 and each generating a substantially uniform field within a respective working region 30,32. Typical examples of the uniformity achieved in each region are ±100ppm within a 50mm diameter and 80mm length cylinder for the region 30 and $\pm 10^{-8}$ within a 5mm diameter and 20mm length cylinder for the region 32.

In addition to the main, actively shielded magnet, additional shims etc (not shown) will be provided either in the cryostat or in the room temperature bore 24,26 as required. This will be well understood by a person of ordinary skill in the art and so will not be described further in detail.

Removably inserted into the bore 26 is a NMR RF probe 6 which also contains shim coils and sample injection equipment. Into the bore 24 is inserted a UHV ICR cell and sample injection equipment 5. The cell 5 and probe 6 will be connected to the other equipment as shown in Figure 1.

In operation, magnetic fields of the desired strength and uniformity can be produced simultaneously in the working volumes 30,32 so that the FTICR and NMR experiments can be carried out on the samples simultaneously.

Figures 3A and 3B illustrate a second example. In this example, the basic construction of the cryostat is the same as in the Figure 2 example and will not be described further. The difference between the two

examples is that a single room temperature bore 34 having a substantially constant cross-section is provided and a single working region 36 having a substantially uniform magnetic field is generated by the magnet assembly 28. The ICR cell probe 5 and the NMR probe 6 are simultaneously located in the bore 34 but only one can be brought into alignment with the working region 36 at any one time. In Figure 3A, the FTICR cell probe 5 has been brought to bring its sample region into the working region 36 while in Figure 3B the NMR probe 6 has been pushed into the bore sufficiently to bring its sample region into alignment with the working region.

Figures 4A and 4B illustrate a further example similar to the Figure 3 example in which a single working region 40 is produced with a substantially uniform magnetic field by the magnet 28. The difference between this example and the previous example is that the probe 5 defines a central, blind bore 42 into which the NMR RF probe 6 can be inserted. This enables the sample region 44 of the probe 6 and the experimental volume 46 of the probe 5 to be made axially coincident.

CLAIMS

1. Sample inspection apparatus comprising a magnet assembly located in a cryostat and surrounding a bore at room temperature so as to define one or more working regions in the bore; a first, NMR probe which can be inserted in the bore to bring a sample into the or one of the working regions, the magnetic field in that working region having a homogeneity or profile suitable for performing a NMR experiment; and a second probe which can be inserted in the bore to bring a sample into the or another working region, the magnetic field in that working region having a homogeneity or profile suitable for performing a different experiment on the sample.

2. Apparatus according to claim 1, wherein the probes are insertable into opposite ends of the bore.

3. Apparatus according to claim 1 or claim 2, wherein two working regions are defined in the bore, the working regions being laterally spaced apart along the bore.

4. Apparatus according to claim 3, wherein the magnet assembly comprises a single magnet.

5. Apparatus according to claim 3 or claim 4, wherein the magnet assembly is controllable to generate the required magnetic fields in each working region simultaneously.

6. Apparatus according to claim 1 or claim 2, wherein a single working region is provided, the probes being constructed so that both can bring their respective samples into the same working region simultaneously.

7. Apparatus according to claim 6, wherein the probes are constructed with male and female ends which interengage.

8. Apparatus according to any of claims 5 to 7, further comprising a system for supplying portions of a sample to each probe from a common source.

9. Apparatus according to claim 8, wherein the common source comprises a liquid chromatograph.

10. Apparatus according to claim 1 or claim 2, wherein a single working region is defined in the bore, each probe

being fully removable from the bore to allow the other probe to be inserted.

11. Apparatus according to any of the preceding claims, wherein the second probe is suitable for use in ion cyclotron resonance mass spectroscopy.

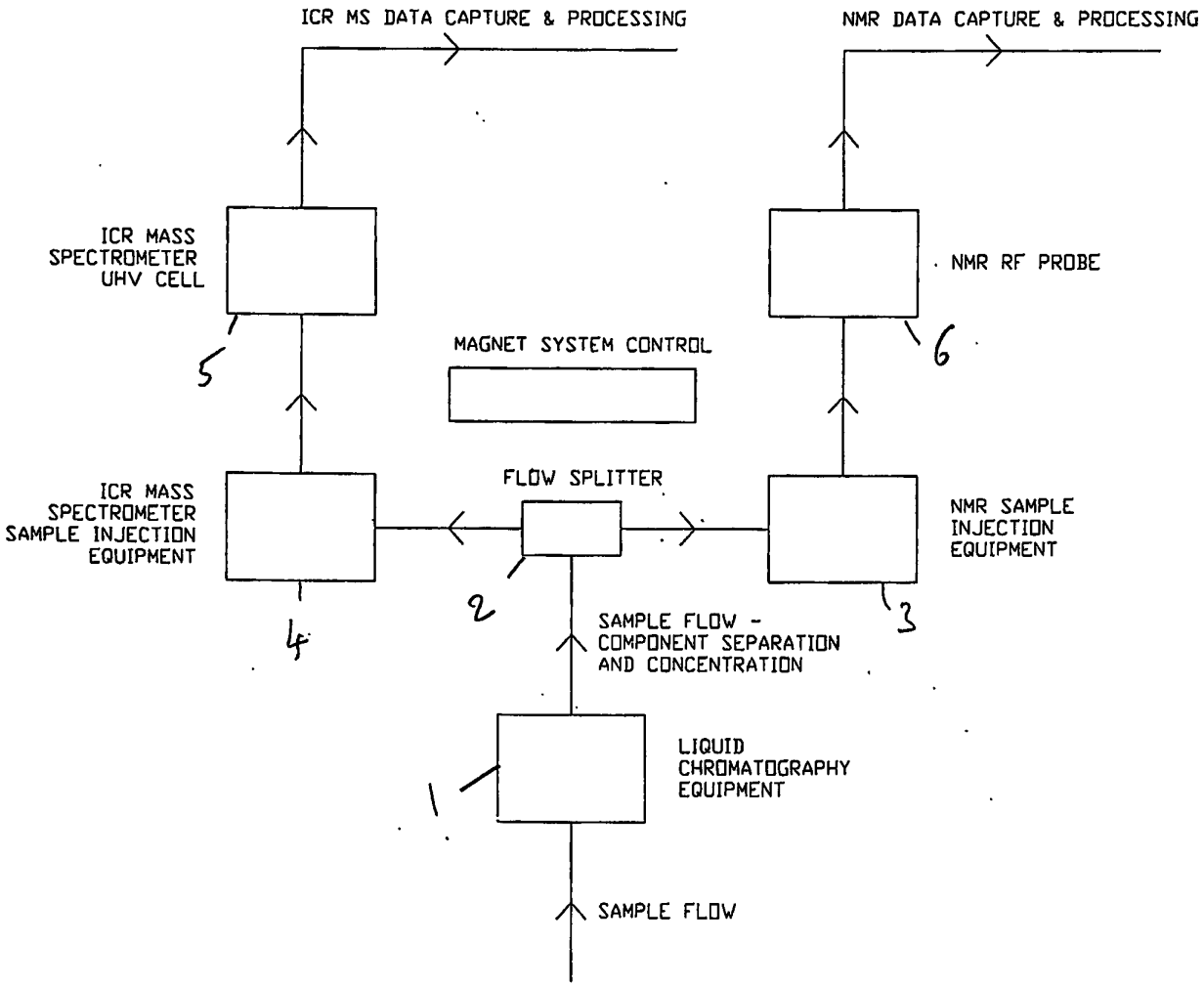

ICR MS DATA CAPTURE & PROCESSING
NMR DATA CAPTURE & PROCESSING
ICR MASS SPECTROMETER UHV CELL
NMR RF PROBE
MAGNET SYSTEM CONTROL
FLOW SPLITTER
ICR MASS SPECTROMETER SAMPLE INJECTION EQUIPMENT
NMR SAMPLE INJECTION EQUIPMENT
SAMPLE FLOW - COMPONENT SEPARATION AND CONCENTRATION
LIQUID CHROMATOGRAPHY EQUIPMENT
SAMPLE FLOW
5
6
4
2
3
1

FIG 1

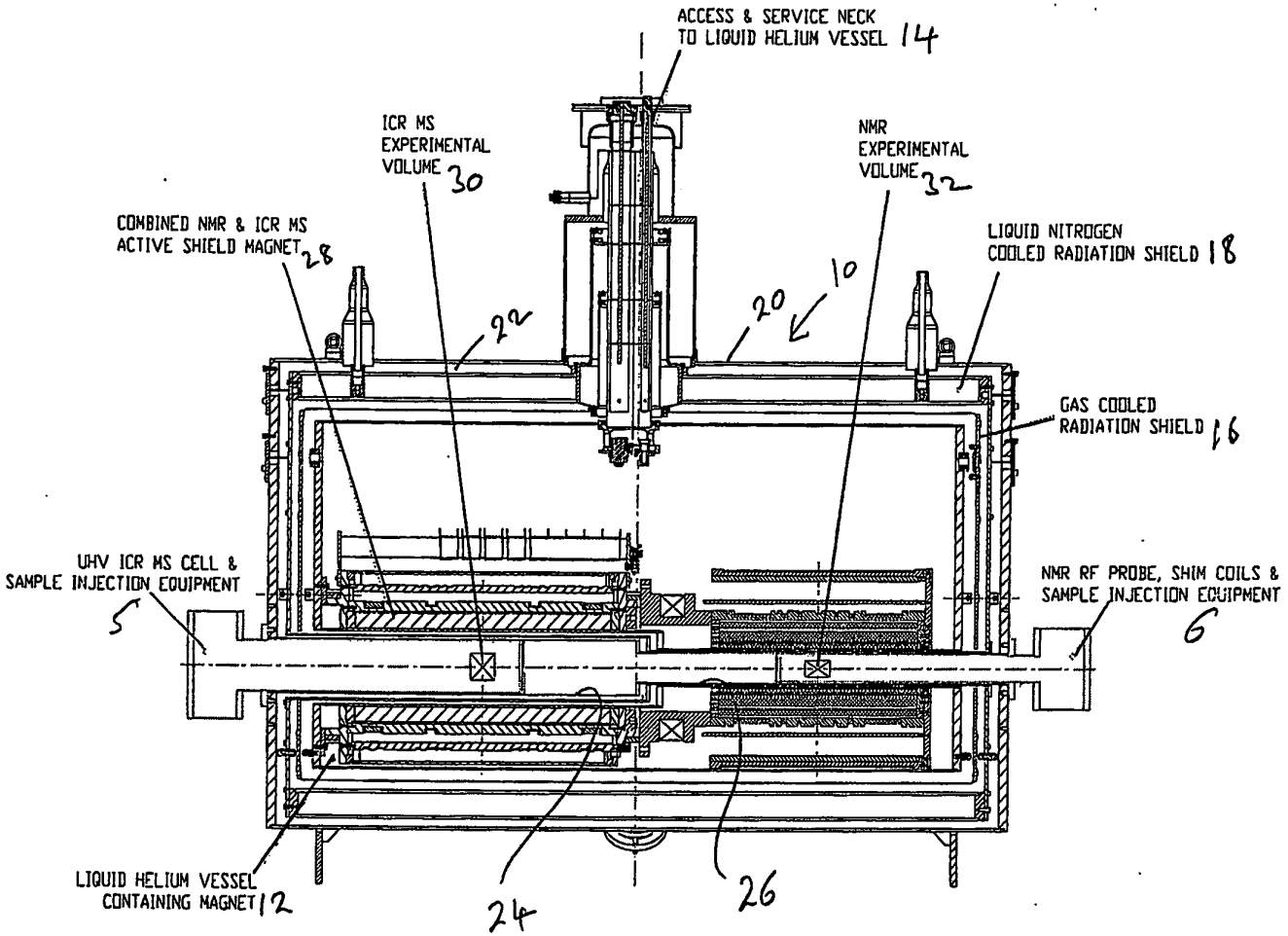
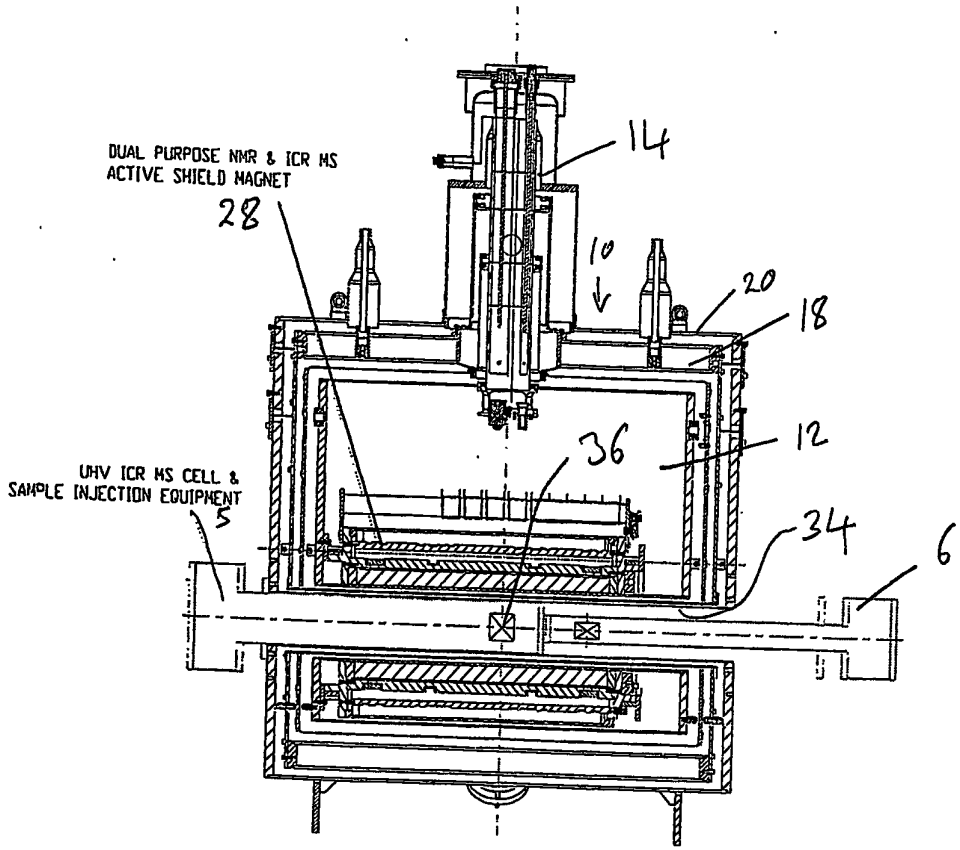
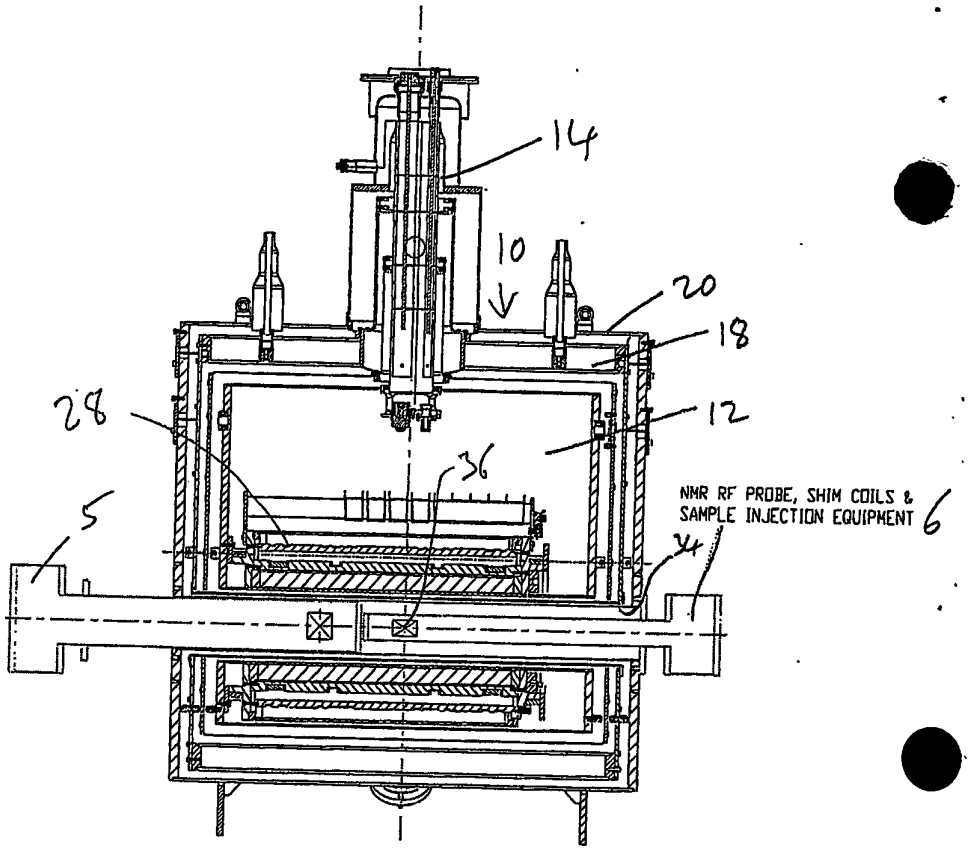

ACCESS & SERVICE NECK
TO LIQUID HELIUM VESSEL 14
ICR MS
EXPERIMENTAL
VOLUME 30
NMR
EXPERIMENTAL
VOLUME 32
COMBINED NMR & ICR MS
ACTIVE SHIELD MAGNET 28
LIQUID NITROGEN
COOLED RADIATION SHIELD 18
22
20
10
GAS COOLED
RADIATION SHIELD 16
UHV ICR MS CELL &
SAMPLE INJECTION EQUIPMENT
5
NMR RF PROBE, SHIM COILS &
SAMPLE INJECTION EQUIPMENT
6
LIQUID HELIUM VESSEL
CONTAINING MAGNET 12
24
26

FIG 2



CONFIGURATION 1 – ICR MS MEASUREMENT

(A)



CONFIGURATION 2 – NMR MEASUREMENT

(B)

FIG 3

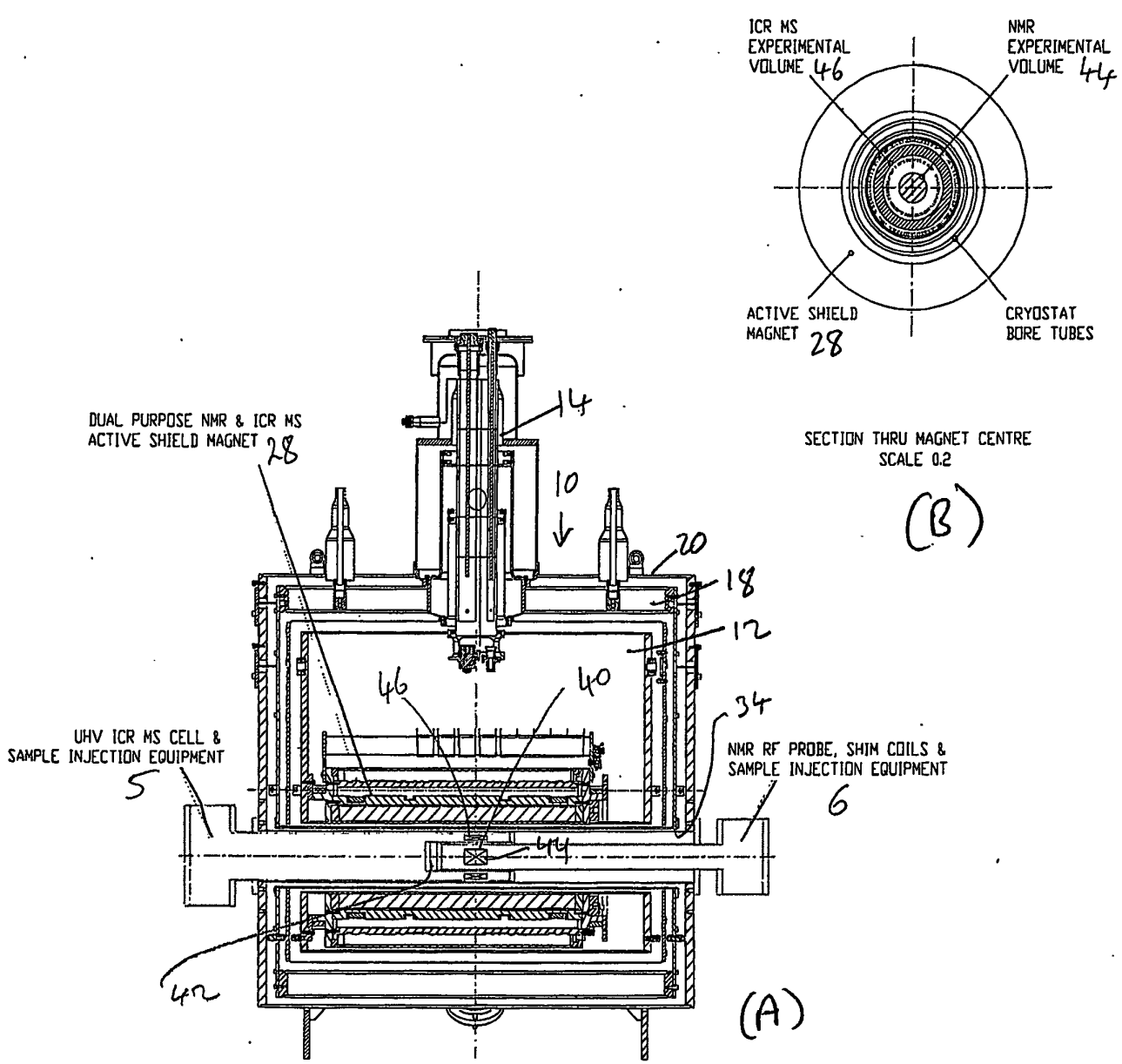

ICR MS
EXPERIMENTAL
VOLUME 46
NMR
EXPERIMENTAL
VOLUME 44
ACTIVE SHIELD
MAGNET 28
CRYOSTAT
BORE TUBES
SECTION THRU MAGNET CENTRE
SCALE 0.2
(B)
DUAL PURPOSE NMR & ICR MS
ACTIVE SHIELD MAGNET 28
14
10
20
18
12
46
40
34
UHV ICR MS CELL &
SAMPLE INJECTION EQUIPMENT
5
NMR RF PROBE, SHIM COILS &
SAMPLE INJECTION EQUIPMENT
6
44
42
(A)

FIG 4